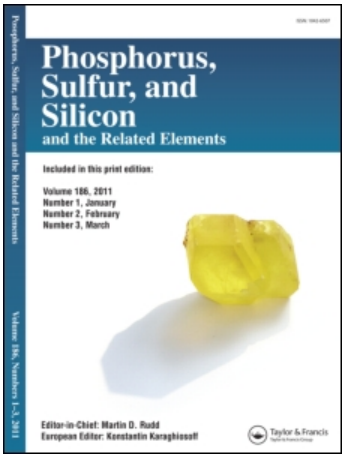

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COMMUNICATION

SYNTHESIS OF CHIRAL THIOCARBAMOYLPHOSPHINES DERIVED FROM AMINO ACIDS[1]

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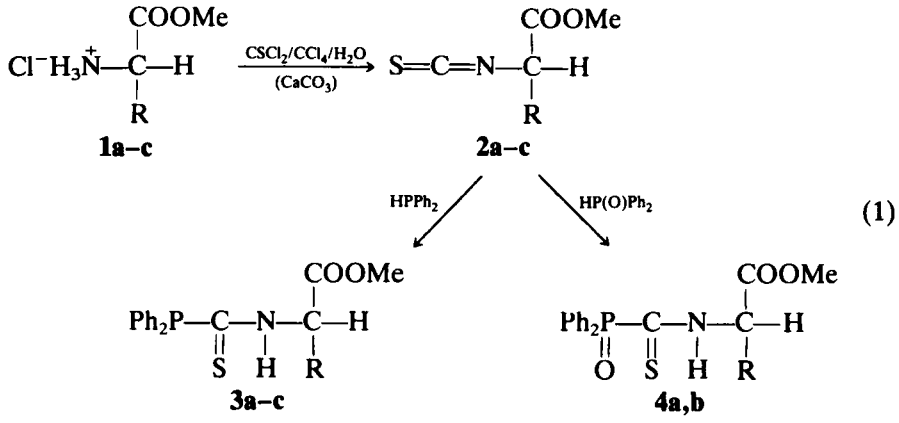
The methylester hydrochlorides of the (*S*)-amino acids L-alanine (**1a**), L-phenylalanine (**1b**), L-valine (**1c**) and L-lysine (**1d**) were converted to the corresponding isothiocyanates **2a–d** by thiophosgenation. **2a–d** react with secondary phosphines and phosphine oxides to give the thiocarbamoylphosphines **3a–d** and *P*-oxides **4a**, **b**.

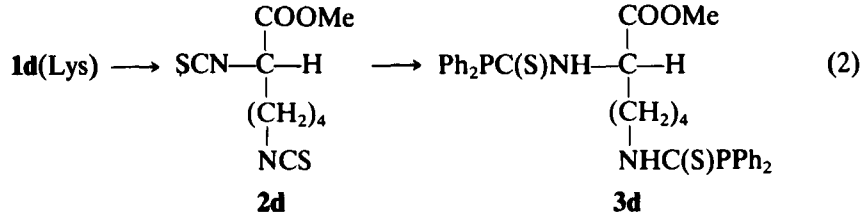
Thiocarbonyl chloride has been widely applied as a versatile reagent in organic synthesis,[2] among others, to convert primary amines into isothiocyanates.[3] The transformation of racemic amino acids was reported by Floch and Kováč.[4] In this communication, we describe the conversion of chiral isothiocyanates derived from naturally occurring amino acids into thiocarbamoylphosphines (phosphinothioformamides) which have been used as ambidentate, stereoselective complex ligands.[5] Since the previously reported transformation of primary amines with carbon disulfide and *N,N*-dicyclohexyl carbodiimide[6] is unapt for amino acid derivatives, the thiophosgenation has approved to be the method of choice. It comprises the further advantage of negligible interference of other functional groups like OH, NH_2, COOR, SO_2NR_2 and is also applicable to diamino carboxylic acids.

The commercially available (*S*)-configurated L-amino acids were protected by esterification according to standard methods.[3,7] The methylester hydrochlorides **1a–d** are dissolved in water and treated with thiocarbonyl chloride.[3,4] The liquid



(1)

1–4	a	b	c
R	CH_3 (Ala)	$C_6H_5CH_2$ (Phe)	$(CH_3)_2CH$ (Val)



(2)

isothiocyanates **2a–d** are separated and purified by vacuum distillation. **2a–d** react with equivalent amounts of diphenylphosphine and diphenylphosphine oxide, respectively, to give the thiocarbamoylphosphines **3a–d** and **4a, b** in quantitative yields. The completeness of conversion was monitored by I.R. spectroscopy. Relevant analytical and spectroscopic data are collected in Table I.

The results show that the transformation of (*S*)-amino acids into thiocarbamoylphosphines proceeds stereospecifically except of L-lysine. In this case, probably thermal racemisation takes place during distillation of the isothiocyanate.

TABLE I

Analytical and spectroscopic data of the isothiocyanates **2a–d** and thiocarbamoylphosphines **3a–d, 4a, b**[a]

Educt	Product	b.p. [°C] (0.1 mbar)	$[\alpha]_D^{20}$[°][b]	I.R.[c] ν[cm^{-1}]	^{1}H-N.M.R.[d] δ[ppm](*J*[Hz])	^{31}P{^{1}H}-N.M.R.[e] δ[ppm]
1a (Ala)	**2a**	41–42	+30.2	2065 (CN) 1745 (CO)	1.55 (d, 7.1, 3H, CH_3-*C**); 3.77 (*s*, 3H, CH_3-*O*); 4.33 (qua, 7.1, 1H, *CH)	
1b (Phe)	**2b**	126	−72.2	2072 1749	3.0–3.4 (m[f], 2H, CH_2); 3.79 (s, 3H, CH_3-*O*); 4.48 (mc, 1H, *CH); 7.2–7.4 (m, 5H, C_6H_5)	
1c (Val)	**2c**	60–61	+41.4	2078 1745	0.95 (d, 6.8, 3H, CH_3); 1.04 (d, 7.0, 3H, CH_3); 2.30 (mc, 1H, CH); 3.77 (s, 3H, CH_3-*O*); 4.14 (d, 4.2, 1H, *CH)	
1d (Lys)	**2d**	160	—	2178 sh 2086 1748	1.3–2.1 (m, 6H, $(CH_2)_3$-*C**); 3.54 (t, 6.1, 2H, CH_2-*N*); 3.81 (s, 3H, CH_3-*O*); 4.31 (t, 6.0, 1H, *CH)	
2a	**3a**	oil	−13.0	3326 (NH) 1739 (CO) 1489 (NCS) 1358 (NCS)	1.45 (d, 7.1, 3H, CH_3-*C**); 3.72 s, 3H, CH_3-*O*); 5.20 (mc[g], 1H, *CH); 7.34–7.64 (m, 10H, C_6H_5)	17.2

TABLE I (*continued*)

Educt	Product	b.p. [°C] (0.1 mbar)	$[\alpha]_D^{20}$[°][b]	I.R.[c] ν[cm^{-1}]	^{1}H-N.M.R.[d] δ[ppm](J[Hz])	^{31}P{^{1}H}-N.M.R.[e] δ[ppm]
2b	**3b**	oil	+50.4	3334 1740 1483 1357	3.20 (mc[h], 2H, CH_2); 3.71 (s, 3H, CH_3-O); 5.50 (mc, 1H, *CH); 6.82–7.57 (m, 15H, C_6H_5)	16.7
2c	**3c**	oil	+23.3	3328 1735 1490 1365	0.72 (d, 7.2, 3H, CH_3); 0.81 (d, 7.3, 3H, CH_3); 2.26 (mc, 1H, CH); 3.70 (s, 3H, CH_3-O); 5.14 (dd, 8.0, 4.4, 1H, *CH); 7.36– 7.68 (m, 10H, C_6H_5)	16.4
2d	**3d**	42–43[i]	—	3339 1737 1491 1347	1.1–2.1 (m, 6H, $(CH_2)_3$- C*); 3.6–3.8 (m, 2H, CH_2-N); 3.69 (s, 3H, CH_3-O); 5.18 (mc, 1H, *CH); 7.40–7.73 (m, 20H, C_6H_5)	16.6 17.5
2a	**4a**	(r.t.)[i]	−27.1	3139 1742 1512 1375 1185 (PO)	1.60 (d, 7.4, 3H, CH_3- C*); 3.76 s, 3H, CH_3-O); 5.13 (mc[g], 1H, *CH); 7.3–8.1 (m, 10H, C_6H_5); 9.95 (b, 1H, NH)	18.3
2b	**4b**	96–97[i]	+56.7	3122 1739 1509 1368 1174	3.31 (mc[k], 2H, CH_2); 3.72 (s, 3H, CH_3-O); 5.48 (mc, 1H, *CH); 7.0–8.0 (m, 15H, C_6H_5); 9.95 (b, 1H, NH)	18.4

[a] Satisfactory microanalyses were obtained for **3a–d** and **4a, b**. ^{13}C-N.M.R. data are also available for **3a–d**. [b] Specific rotation (sol. toluene, conc. ca. 10 mg · ml^{-1}) recorded with Perkin–Elmer polarimeter 241 MC. [c] Perkin–Elmer IR spectrophotometer 598 with data station 3600 (film; **3d**, **4b**: KBr pellet). [d] Bruker WP 80 multinuclear spectrometer (sol. $CDCl_3$, int. TMS). [e] Bruker WP 80 (sol. tetrahydrofuran, ext. H_3PO_4/H_2O). [f] ABX spin system: δ_A 3.13, δ_B 3.25, δ_X 4.48 ppm; J_{AX} 8.7, J_{BX} 4.4, J_{AB} 13.8 Hz. [g] Pseudo-quintet, $J(CH\text{-}NH) \approx J(CH\text{-}CH_3)$ (7.1 Hz). [h] ABX spin system: δ_A 3.07, δ_B 3.34, δ_X 5.50 ppm; J_{AX} 6.1, J_{BX} 5.4, J_{AB} 14.1 Hz. [i] m.p. (from methanol). [k] ABX spin system: δ_A 3.22, δ_B 3.40, δ_X 5.48 ppm; J_{AX} 6.7, J_{BX} 5.5, J_{AB} 13.8 Hz.

EXPERIMENTAL

Synthesis of Diphenyl[N-(1-carboxymethyl)alkyl]thiocarbamoylphosphines **3a–d** *and P-oxides* **4a, b**; *General Procedure*:

Esterification.[7] Thionyl chloride (7.9 ml, 0.11 mol) is added dropwise to dry methanol (30 ml, 0.78 mol) at 0°C. The L-amino acid (0.1 mol) is added in small portions and the solution stirred for 1–2 days. The ester hydrochlorides **1a–c** are obtained after evaporation of the solvent as white solids which were dried on the vacuum pump. In case of L-lysine, additional refluxing for 10 h is required, and **1d** is precipitated as colourless needles on cooling.

Thiophosgenation.[4] **1a–d** (50 mmol) are dissolved in water (10–15 ml). A layer of calcium carbonate (10 g, 100 mmol; **1d**: 20 g) and carbon tetrachloride (20 ml) is added to the solution. Then thiocarbonyl chloride (5 ml, 15% molar excess; **1d**: 10 ml) is added dropwise, and the mixture is stirred for 10 h at room temperature. After filtration of excessive calcium carbonate and evaporation of the organic solvent, the yellow residue is distilled *in vacuo* to give **2a–d** as colourless liquids in 50–80% yield (**2d**: 30%).

Phosphinylation.[6] Equimolar amounts of **2a–c** (5–10 mmol) and diphenylphosphine (0.85–1.7 ml) (**2d**: molar ratio 1/2) are mixed without a solvent and then kept for 2–3 days at 40°C. The resulting thiocarbamoylphosphines **3a–d** are obtained quantitatively as yellow oils which are purified by

TABLE II

Microanalyses and molar mass (MS, FD method) of **3a–d** and **4a, b**

Compd.	Analyses calc. found	C	H	N	S	Formula	Molar mass
3a		61.62	5.48	4.23	9.68	$C_{17}H_{18}NO_2PS$	331.37
		61.84	5.57	4.09	9.81		331
3b		67.80	5.44	3.44	7.87	$C_{23}H_{22}NO_2PS$	407.47
		67.44	5.43	3.36	7.93		407
3c		63.49	6.17	3.90	8.92	$C_{19}H_{22}NO_2PS$	359.43
		63.58	6.72	3.89	9.04		359
3d		64.27	5.56	4.54	10.40	$C_{33}H_{34}N_2O_2P_2S_2$	616.72
		63.29	5.72	4.46	10.37		616
4a		58.78	5.22	4.03	9.23	$C_{17}H_{18}NO_3PS$	347.37
		58.53	5.36	3.90	9.07		347
4b		65.23	5.24	3.30	7.57	$C_{23}H_{22}NO_3PS$	423.47
		66.58	5.73	2.47	7.20		423

washing with *n*-hexane (**3a–c**) or recrystallisation from methanol (**3d**). For the preparation of the *P*-oxides, equimolar amounts of **1a, b** and diphenylphosphine oxide are dissolved in diethyl ether and kept on reflux for 24 h. After filtration, *n*-hexane is added to the solution where **4a, b** crystallize at −30°C (yield 70%). The microanalytical data of **3a–d** and **4a, b** are collected in Table II.

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